globinuria who was also heterozygous for the two variants of glucose-6-phosphate dehydrogenase (G6PD) was confirmed by finding that the red cells showing the paroxysmal nocturnal haemoglobinuria defect had a single-enzyme phenotype while the normal red cells had a double-enzyme phenotype.[13] Another patient presented with paroxysmal nocturnal haemoglobinuria and erythroleukaemia and only the neoplastic clone had the paroxysmal nocturnal haemoglobinuria abnormality.[14] The abnormality in granulocytes is also thought to be clonal.[3 4] The paroxysmal nocturnal haemoglobinuria clone may arise in a normal marrow or in one which is already abnormal. The abnormal clone may not persist but may gradually disappear with time and, rarely, patients with paroxysmal nocturnal haemoglobinuria develop aplastic anaemia. Indeed, the similarities between paroxysmal nocturnal haemoglobinuria and aplastic anaemia have been emphasised by Dacie and Lewis[15] and the myelodysplastic syndromes, including paroxysmal nocturnal haemoglobinuria and aplastic anaemia, share the tendency to transform to acute leukaemia.

Paroxysmal nocturnal haemoglobinuria is usually treated symptomatically. Nevertheless, the only definitive treatments for stem-cell disorders such as paroxysmal nocturnal haemoglobinuria are to alter or replace the abnormal stem-cell population. Stem-cell proliferation has not yet been altered beneficially but normal stem cells can be provided by bone marrow transplantation. A patient with paroxysmal nocturnal haemoglobinuria complicated by refractory marrow failure has been treated successfully by infusion of normal bone marrow.[16] Since the donor was an identical twin, the patient did not require immunosuppression before receiving the cells but, despite the lack of treatment directed against the abnormal clone, the abnormal cells were displaced by the normal bone marrow. Transplantation of allogeneic bone marrow has also been successful in the treatment of paroxysmal nocturnal haemoglobinuria.[17 18] Nevertheless, at present the hazards of allogeneic bone marrow grafting stand in the way of justifying transplantation as the treatment of choice for patients with paroxysmal nocturnal haemoglobinuria, who may live for years with conventional supportive treatment.

[1] Rosse WF, Dacie JV. Immune lysis of normal human and paroxysmal nocturnal hemoglobinuria (PNH) red blood cells. I. The sensitivity of PNH red cells to lysis by complement and specific antibody. *J Clin Invest* 1966;**45**:736-48.

[2] Aster RH, Enright SE. A platelet and granulocyte membrane defect in paroxysmal nocturnal hemoglobinuria: usefulness for the detection of platelet antibodies. *J Clin Invest* 1969;**45**:1199-210.

[3] Brubaker LH, Essig Le RJ, Mengel CE. Neutrophil life span in paroxysmal nocturnal hemoglobinuria. *Blood* 1977;**50**:657-62.

[4] Stern M, Rosse WF. Two populations of granulocytes in paroxysmal nocturnal hemoglobinuria. *Blood* 1979;**53**:928-34.

[5] Craddock PR, Fehr J, Jacob HS. Complement-mediated granulocyte dysfunction in paroxysmal nocturnal hemoglobinuria. *Blood* 1976;**47**: 931-9.

[6] Tumen J, Kline LB, Fay JW, *et al.* Complement-sensitivity of paroxysmal nocturnal hemoglobinuria bone marrow cells. *Blood* 1980;**55**:1040-6.

[7] Charache S. Prolonged survival in paroxysmal nocturnal hemoglobinuria. *Blood* 1969;**33**:877-83.

[8] Dacie JV. *The haemolytic anaemias: congenital and acquired.* Part IV. London: J and A Churchill, 1967.

[9] Peytremann R, Rhodes RS, Hartmann RC. Thrombosis in paroxysmal nocturnal hemoglobinuria (PNH) with particular reference to progressive, diffuse hepatic venous thrombosis. *Series Haematologica* 1972;**5**:115-36.

[10] Clarke DA, Butler SA, Braren V, Hartmann RC, Jenkins DEJ. The kidneys in paroxysmal nocturnal hemoglobinuria. *Blood* 1981;**57**:83-9.

[11] Polli E, Sirchia G, Ferrone S, Mercuriale F, Zanella A. *Emoglobinuria parossotica notturna—revisione critica.* Milan: Edizione Cilag-Chemie Italiana, 1973.

[12] Kaye D, Hook EW. The influence of hemolysis or blood loss on susceptibility to infection. *J Immunol* 1963;**91**:65-75.

[13] Oni SB, Osunkoya BO, Luzzatto L. Paroxysmal nocturnal hemoglobinuria: evidence for monoclonal origin of abnormal blood cells. *Blood* 1970; **36**:145-52.

[14] Luzzatto L, Familusi JB, Williams CK, Junaid TA, Rotoli B, Alfinito F. The PNH abnormality in myeloproliferative disorders: association of PNH and acute erythremic myelosis in two children. *Haematologica (Pavia)* 1979;**64**:13-30.

[15] Dacie JV, Lewis SM. Paroxysmal nocturnal haemoglobinuria: variation in clinical severity and association with bone-marrow hypoplasia. *Br J Haematol* 1961;**7**:442-57.

[16] Fefer A, Freeman H, Storb R, *et al.* Paroxysmal nocturnal hemoglobinuria and marrow failure treated by infusion of marrow from an identical twin. *Ann Intern Med* 1976;**84**:692-5.

[17] Storb R, Thomas ED, Weiden PL, *et al.* Aplastic anemia treated by allogeneic bone marrow transplantation: a report on 49 new cases from Seattle. *Blood* 1976;**48**:817-41.

[18] Hows JM, Harris R, Palmer S, Gordon-Smith EC. Immunosuppression with cyclosporin A in allogeneic bone marrow transplantation for severe aplastic anaemia—preliminary results. *Br J Haematol* (in press).

Research in the NHS

The difficulties encountered by NHS doctors in doing clinical research were the subject of a half-day seminar in Oxford last month, organised by the research committee of the Oxfordshire AHA(T). The origins of the seminar lay in the growing awareness among doctors in the Oxfordshire area of the difficulty of carrying out good research, and indeed much of the meeting was taken up with a catalogue of problems. Predictably, many of these concerned the inadequacy of resources, particularly time, laboratory space, and the skills of ancillary workers. Speakers also drew attention to NHS doctors' uncertainties about their participation in research, the discouraging attitudes of some senior managers and authority members, and the difficulties that doctors might face in seeking help or collaboration from their local university. While no one suggested that health authorities should assume total responsibility for providing doctors with the resources needed for their research, several speakers argued that a more helpful and encouraging attitude by the authorities would not come amiss.

At a deeper level of analysis the seminar considered the hallmarks of good research and the preconditions for its attainment. Some speakers, particularly those with outstanding records of research achievement themselves, argued that if high standards were to be maintained research workers must be trained properly through early exposure to the rigorous demands of the scientific method and must be insulated from all the diversionary influences that detracted from a serious and dedicated commitment to a research career. Several factors were identified that militated against the training of good researchers in the NHS, including the rigid structures of specialist training that inhibited the development of an inquisitive mind, the sheer pressures of clinical work that often relegated research to the status of a spare-time activity, and the attractions of early promotion to a consultant post.

Other speakers rejected this approach as excessively purist, suggesting instead that research was an integral part of self-education and should thus be pursued by all doctors. There was a place, they claimed, for the careful collection and analysis of simple data as well as the theoretical and methodological complexities of advanced research, and the former needed encouraging and funding as much as the latter. The locally organised research scheme operated by the health authorities was regarded as a valuable way of promoting research, not only in providing funds (some £4m in the current financial year) but also in exposing research ideas and proposals to the critical appraisal of colleagues. Interestingly, however, the needs and experiences of general practitioners were not raised at all in the

seminar, though they have equal access to funds in the locally organised research scheme and presumably encounter similar problems to those of hospital doctors.

Understandably, the seminar was better at identifying problems than at suggesting solutions, but a few kites were flown. The attitudes of NHS managers and of health authority members may be difficult to change, but one plan that would enhance the status of NHS research would be the hypothecation of specified sums for research purposes only from the money being redistributed under the RAWP scheme and linked to a system of monitoring the quality of work done. Another, more forceful suggestion was that the present permissive powers of health authorities to provide background support for clinical research should become mandatory and might be linked to the designation of a certain number of NHS beds for research purposes. Yet perhaps the most important contribution of the seminar was simply the opening up of these issues for debate, and the Oxfordshire Research Committee is to be applauded for its initiative.

Antibiotic-associated colitis —the continuing saga

Clostridium difficile and its toxin were first found in patients with antibiotic-associated colitis in 1978.[1-3] Antimicrobial treatment, by suppressing normal gut flora, is now thought to make some patients susceptible to colitis caused by this toxin. The origin of the infection is still uncertain, since the organism is probably carried by only a few people: *C difficile* has been found in the stools of less than 2% of healthy adults,[4] though possibly very small numbers of the bacteria may be undetected even with selective media. Some clustering of cases[5-7] suggests that cross-infection may be important—a theory borne out by experimental studies in hamsters, which when given clindamycin develop fatal inflammatory lesions of the ileum and caecum (similar in many respects to human pseudomembranous colitis), though only if *C difficile* is acquired from their environment.[3]

The antibiotics incriminated most frequently are clindamycin and lincomycin, which accounted for 80% of reports submitted to the Committee on Safety of Medicines from 1964 to 1978.[8] Ampicillin, tetracycline, chloramphenicol, cephalosporins, penicillin, co-trimoxazole, and metronidazole have also been implicated, ampicillin more often than the others.[9] The predominance of clindamycin probably reflects its potent activity against faecal anaerobes, which are noticeably suppressed in patients with pseudomembranous colitis.[10] Antibiotics that deplete the gut flora in this way may promote the proliferation of *C difficile* and lead to production of its toxin, which induces necrotising lesions in colonic mucosa. Physiological disturbances caused by ischaemia, neoplasms, or inflammation may make patients particularly vulnerable and probably contribute to the greater frequency of severe antibiotic-associated colitis in the elderly.

Neither duration of chemotherapy nor dose appears to influence the likelihood of colitis—even short courses of surgical prophylaxis have been implicated. There may, however, be an interval as long as four weeks between stopping an antibiotic and the onset of symptoms. Toxigenic strains of *C difficile* are usually resistant to many antibiotics; 30-40% are resistant to clindamycin[3 11]—and isolates from patients with antibiotic-associated colitis induced by clindamycin are invariably resistant. Selection of clindamycin-resistant strains seems likely to be promoted by widespread use of clindamycin in a community, especially if the organism can be transmitted from patient to patient (perhaps by means of equipment such as bed pans or sigmoidoscopes).

What are the important aspects of management? Early recognition is vital, and though the clinical presentation is not particularly distinctive certain features may alert the physician. Typically, a patient recently treated with antibiotics develops watery diarrhoea, sometimes with severe abdominal pain, fever, and leucocytosis.[12] Sigmoidoscopy and biopsy may be helpful, though some patients with pseudomembranous lesions in the colon lack typical changes in the rectum.[13] The presence of a faecal toxin neutralised by *C sordelli* antitoxin is diagnostic, and toxic effects are detectable in tissue culture usually within 24 hours. A Birmingham team, reviewing 66 cases of antibiotic-associated colitis,[12] confirmed the diagnosis by sigmoidoscopy in 49% of cases, histologically in 68%, and by detection of toxin in 78%. *C difficile* was cultured from almost 90% of patients, though in the absence of toxin isolation of the organism is not considered diagnostic.

Treatment with oral vancomycin has usually proved safe and effective, producing rapid resolution of symptoms and elimination of both *C difficile* and its toxin.[14] Vancomycin is effective where clostridial toxin has been identified but not in patients with other varieties of postoperative diarrhoea.[15] The best dose and length of course have still not been established, but doses of 125 mg six-hourly produce faecal concentrations much greater than the minimum required for killing *C difficile*[15]; they are usually given for five days. Vancomycin should be started as soon as possible, since damage from the toxin may not be reversed by chemotherapy.[16] In most cases withdrawal of antibiotics is also rational (indeed, some patients respond readily to this measure alone), though in some the treatment of a primary life-threatening infection is essential. Such patients should probably be switched to another antibiotic, with a narrow-spectrum activity against a known or likely pathogen.

Relapses have been reported,[17 18] and a persistent carrier state has been discovered in some patients who have had clostridial antibiotic-associated colitis.[5] *C difficile* is a spore-bearing organism whose spores may survive an initial five-day treatment with vancomycin to germinate after the course has been completed. These organisms remain susceptible to vancomycin, and possibly a second course of vancomycin should be given to destroy any residual pathogens. Patients who have had antibiotic-associated colitis and require further courses of antibiotics may justifiably be covered by vancomycin prophylaxis.[19] One solution to this problem could be development of a toxoid vaccine conferring immunity to *C difficile*. Metronidazole has proved less popular than vancomycin since it is so efficiently absorbed from the gastrointestinal tract that very little drug remains in the gut lumen. It is, however, much cheaper than vancomycin, and has been used successfully.[20]

Patients with antibiotic-associated colitis should be nursed with the same precautions as others with enteric infections. In particular, sigmoidoscopes should be decontaminated by immersion for at least three hours in a sporicidal disinfectant such as glutaraldehyde.

C difficile and its toxin have also been implicated in exacerbations of chronic inflammatory bowel disease.[21-23] Disturbances in the gastrointestinal tract caused by inflammation could perhaps dispose to this infection. Nevertheless, sulphapyridine, a metabolite of sulphasalazine, cannot be entirely dismissed as a possible culprit (it may be particularly important in slow